Mail stop PATENT
Attorney Docket No. 27133U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

KOHL, et al.

Serial No: 10/564,768 Group Art Unit: 1611

Filed: January 17, 2006 Examiner: POLANSKY, G.

For: **ALKALINE SALTS OF PROTON PUMP INHIBITORS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Declaration Under 37 CFR 1.132

1. I, Dr. Bernd Müller, declare and say:

1.1. That I am a citizen of the Federal Republic of Germany, residing at Bücklestr. 84a, 78467 Konstanz, Germany.

1.2. That I am an inventor of the captioned application for U.S. Letters Patent.

1.3. That, I have studied chemistry from 1991-1999 at the University of Konstanz. I received a Diploma in Chemistry in 1996 and a Ph.D. in Organic Chemistry in 1999.

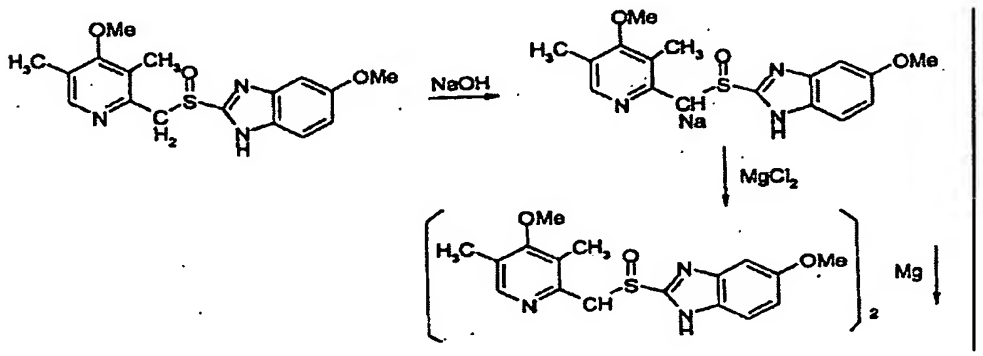
1.4. That, I joined Byk Gulden (renamed to ALTANA Pharma AG, now renamed as Nycomed GmbH) in September of 1999 as a laboratory head in Chemical Development. This department is dedicated to developing technically feasible processes for making large quantities of new compounds designed by medicinal chemists at Byk Gulden / ALTANA Pharma AG / Nycomed GmbH in connection with various research projects. My responsibilities included the supervision of process development for various type of processes like purification processes, salt crystallization, salt conversion, preparation of solvates / hydrates.

2. Traversing the rejections under 35 USC §102(b) and 35 USC §103(a)

2.1 I have studied the Office Action mailed July 3rd, 2008 as well as the cited prior art CN1367172 to Cui et al. and US Patent No. 6,410,569 to Kohl. I am aware that the examiner has rejected claims 1-5 and 7 under 35 U.S.C. 102(b) as being anticipated by CN1367172 to Cui et al. I am also aware that the examiner has rejected claims 1-5, 7, 13 and 14 under 35 U.S.C. 103(a) as being unpatentable over CN1367172 to Cui et al. in view of US Patent No. 6,410,569 to Kohl.

2.2 Cui et al. do not teach anything that would anticipate the subject matter of the pending claims. The disclosure at page 2 of Cui et al. directly points to a pure magnesium salt of the substituted benzimidazole (i.e., omeprazole), which is in contrast to the presently claimed subject matter (see, page 6 of the English translation):

"Said process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol of the present invention is as follows, dissolving the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound into an alkaline aqueous solution, making the pH value of the solution to 9-13, preferably be pH 9-10, then adding into the aqueous solution by dripping a calculated amount of a water-soluble magnesium salt solution, having it thoroughly precipitated and collecting the precipitate so as to obtain the corresponding magnesium salt of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound. By taking the omeprazole magnesium salt as an example its reaction process is as follows:



"

Further, the disclosure at page 3, 3rd paragraph of Cui et al., teaches a ratio of PPI to magnesium of 1 to 0.5 (see, page 7, 2nd paragraph of the English translation):

"Since in the above-mentioned magnesium salt of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound, the theoretically calculated value of molar ratio of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound to magnesium ions in the salification is 1:0.5. Therefore, during said salification of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound and magnesium salt in the alkali aqueous solution, if the added amount of magnesium is less than the calculated amount, it will certainly lead to the incomplete salification; while an excess addition of magnesium will lead to excess production of magnesium hydroxide, which also increases the complication and difficulties of the aftertreatment operation and influences the yield and purity of the required product. The experimental results have shown that, by giving considerations to the two cases, a molar ratio of 1:0.45 to 0.55 of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound to the magnesium ions is generally used as the calculated amount of the dripping aqueous solution mentioned above, which has achieved a satisfactory result."

From this disclosure, it is very clear that Cui et al. do not disclose a compound as presently claimed. The recommended and used ratio of PPI to Mg of 2 : 1 cannot lead to a compound having a ratio of PPI to Mg of 1 : 1, as required for example for the elected species of the presently pending claims.

2.3 This fact is further confirmed by the results of the examples of Cui et al., where almost all of the used PPI is recovered from the reaction mixture. If a compound with a 1:1 ratio of PPI to Mg should have been formed during the described reactions, at maximum only 50% of the used PPI should have been recovered in the precipitate. However, the amounts of PPI precipitated in the Examples of Cui et al. are mostly over 90%. The following overview summarizes the relevant ratios as used in the examples of Cui et al.:

Ex.	PPI / mmol		NaOH / mmol	Mg-salt / mMol	PPI : Mg	Amount of PPI precipitated %
1	S-Ome	14,5	18,76	7,23	2 : 1	98.2
2	S-Ome	14,5	28	7,23	2 : 1	85.0
3	S-Ome	14,5	18,2	7,23	2 : 1	99.1
4	S-Ome	14,5	n.a.	7,23	2 : 1	98.7
5	R/S-Ome	14,5	n.a.	7,23	2 : 1	n.a.
6	Panto	14,2	n.a.	7,08	2 : 1	n.a.
7	S-Ome	86,8	n.a.	43,4	2 : 1	99.1
8	Lanso	13,5	n.a.	6,79	2 : 1	n.a.
9	R-Ome	14,5	n.a.	7,23	2 : 1	98.1

n.a. = not available

2.4 Beside the PPI : Mg ratio, the disclosure of Cui et al. regarding the ratio between PPI and free acid clearly demonstates that the teaching of Cui et al. can not inherently anticipate the subject matter of the presently pending claims. In all of the described examples of Cui et al., the free acid of the PPI is used, which indicates that a hydrogen atom is connected to one of the nitrogen atoms of the benzimidazole moiety of the molecule. In contrast to the disclosed reaction scheme of Cui et al., it is well known that the deprotonation occurs at the benzimidazole moiety of the molecule and not at the methylene group of the sulfinylpyridyl-methyl moiety. One stoichiometric equivalent of sodium hydroxide is necessary to withdraw this hydrogen atom from the benzimidazole moiety. Different from the teaching in Cui et al., the examples of the present application always start from the sodium salt of the PPI, thus omitting the first step of deprotonation of the benzimidazole moiety as required by Cui et al. (withdrawal of hydrogen atom from one of the benzimidazole nitrogens).

2.5 Lastly, there is the disclosure of the physical IR data provided for example 1 of Cui et al. For comparison purposes, a collection of IR spectra of different compounds is herewith enclosed as Exhibit B. The collection shows from top to bottom the IR-spectra of (pantoprazole)$_2$Mg 2xH_2O (as described in the Kohl reference), *rac-*(pantoprazole) OH Mg 1xH_2O (example 1 of the present application), *(S)-*(pantoprazole) OH Mg 1xH_2O (examples 2 and 11 of the present application) and (pantoprazole)$_3$ OH Mg_2 4xH_2O (example 4 of the present application).

2.6 From this comparison it is immediately evident that the IR spectra of the latter three compounds show additional vibrations at around 3700 cm^{-1}, 2370 cm^{-1} and 2345 cm^{-1} which refer to the OH-ion. The IR-spectra of (pantoprazole)$_2$Mg 2xH_2O is plain in these areas of the IR-spectra. Although Cui et al. only provide IR-data for (omeprazole)$_2$Mg (example 1), and although omeprazole has some different substituents at the benzimidazole and pyridyl moieties than pantoprazole, these differences can not have a high influence with respect to the areas around 3700 cm^{-1} and between 2300 and 2400 cm^{-1}. The given data in Cui et al. for (omeprazole)$_2$Mg "FT-IR(KBr)cm^{-1}: 2997.7(Ar), 2949.6, 2835.2(-CH_3, -CH_2-), 1616.2, 1570.0, 1271.2, 1155.2, 1077.6, 839.0" are very similar to the IR spectra of (pantoprazole)$_2$ Mg 2xH_2O from the Kohl reference and clearly indicate that no OH anion is present.

2.7 In view of the above mentioned facts, it is obvious that Cui et al. only describe $(PPI)_2Mg$ compounds. None of the examples of Cui et al. provide any teachings or suggestions which would render the subject matter of the pending claims as anticipated, either expressly or inherently. Accordingly, the rejection of pending claims 1-5 and 7 is improper.

2.8 With respect to the rejection of claims 1-5, 7, 13 and 14 for obviousness, the Kohl reference does not remedy the deficient teachings of the Cui et al. reference. Kohl discloses magnesium pantoprazole dihydrate which is prepared by reacting pantoprazole sodium sesquihydrate with magnesium dichloride hexahydrate in purified water, centrifuging, washing and drying the precipitated solid (see, column 2, lines 45 –67 and the Examples). The reaction is performed without the use of any further hydroxide ions being present in the solution. The same situation applies to the alternative synthesis route as described in the paragraph bridging columns 3 and 4 of Kohl. Additionally, the melting point of pantoprazole magnesium dihydrate as disclosed in Kohl is higher than the melting point of example 1 of the present application, magnesium pantoprazole hydroxyl monohydrate (194-196°C vs. 184-187°C, page 7 top). Accordingly, the compound as disclosed in Kohl is different from the compounds as described and claimed in the present application.

2.9 Further, there are no major differences between the teachings of Cui et al. and Kohl with respect to the final compounds. Both references describe PPI magnesium salts whereby Kohl is limited to pantoprazole as the PPI and further defines the obtained compound to be a dihydrate. However, the ratio between the PPI and Mg in the final products is identical. The main difference with respect to the synthesis paths is that Cui et al. start from the free acid form of the benzimidazoles and Kohl starts from the sodium salt. With respect to the alternative route of Kohl, the reaction is performed in a non-aqueous medium directly with magnesium methanolate (paragraph bridging columns 3 and 4). Since both teachings lead to almost identical compounds, Kohl fails to remedy the deficiencies of Cui et al. There is no guidance to a person of ordinary skill in the art to arrive at the presently claimed compounds, thus providing PPI compounds with an increased stability, based on the Cui et al. and Kohl references. Accordingly, Cui et al., taken alone or in combination with Kohl, does not

teach or suggest the subject matter of the pending claims. As such, the rejection of pending claims 1-5, 7, 13, and 14 is also improper.

3. The undersigned Declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Signed at Constance,
Federal Republic of Germany,

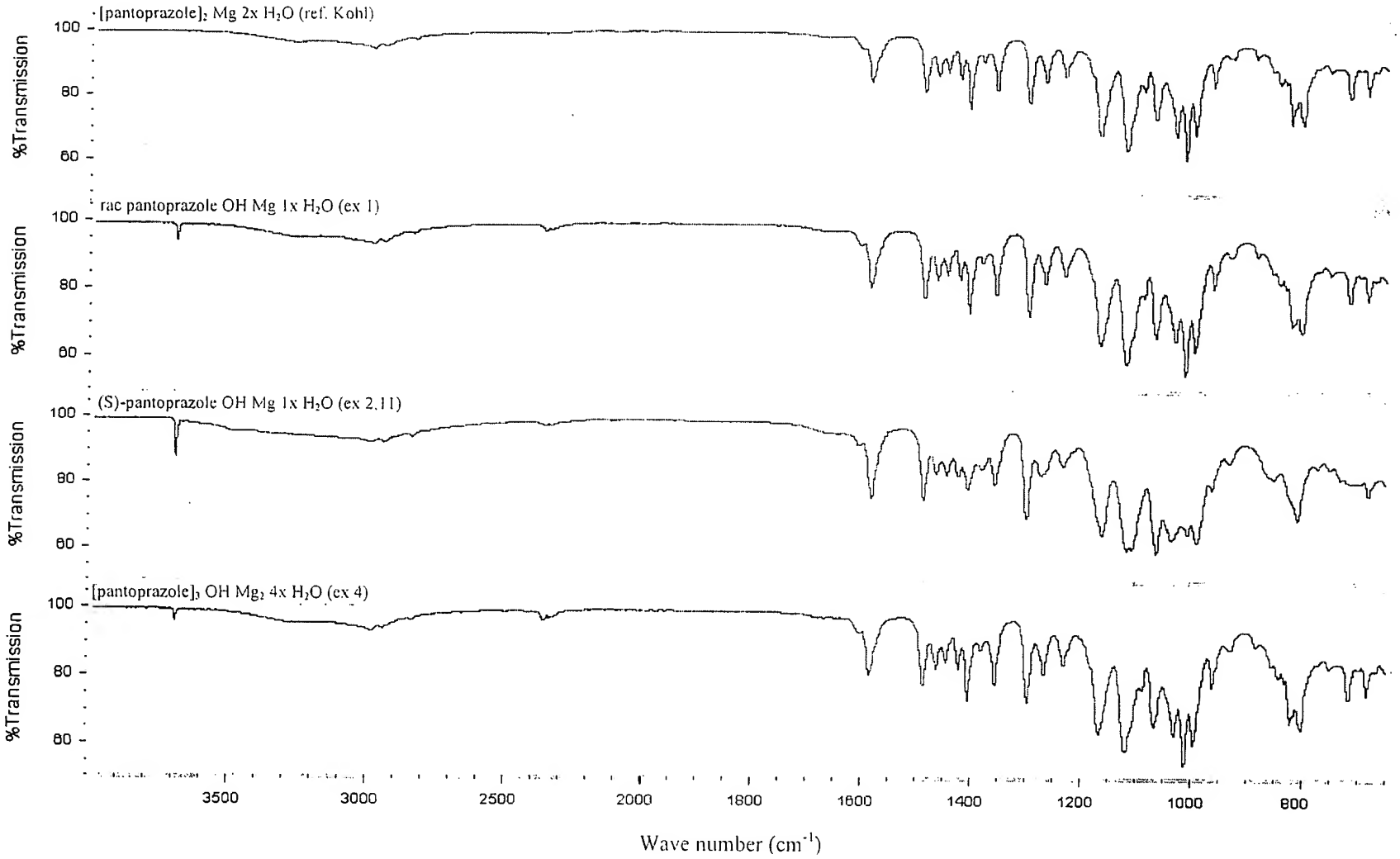
September 26th, 2008.

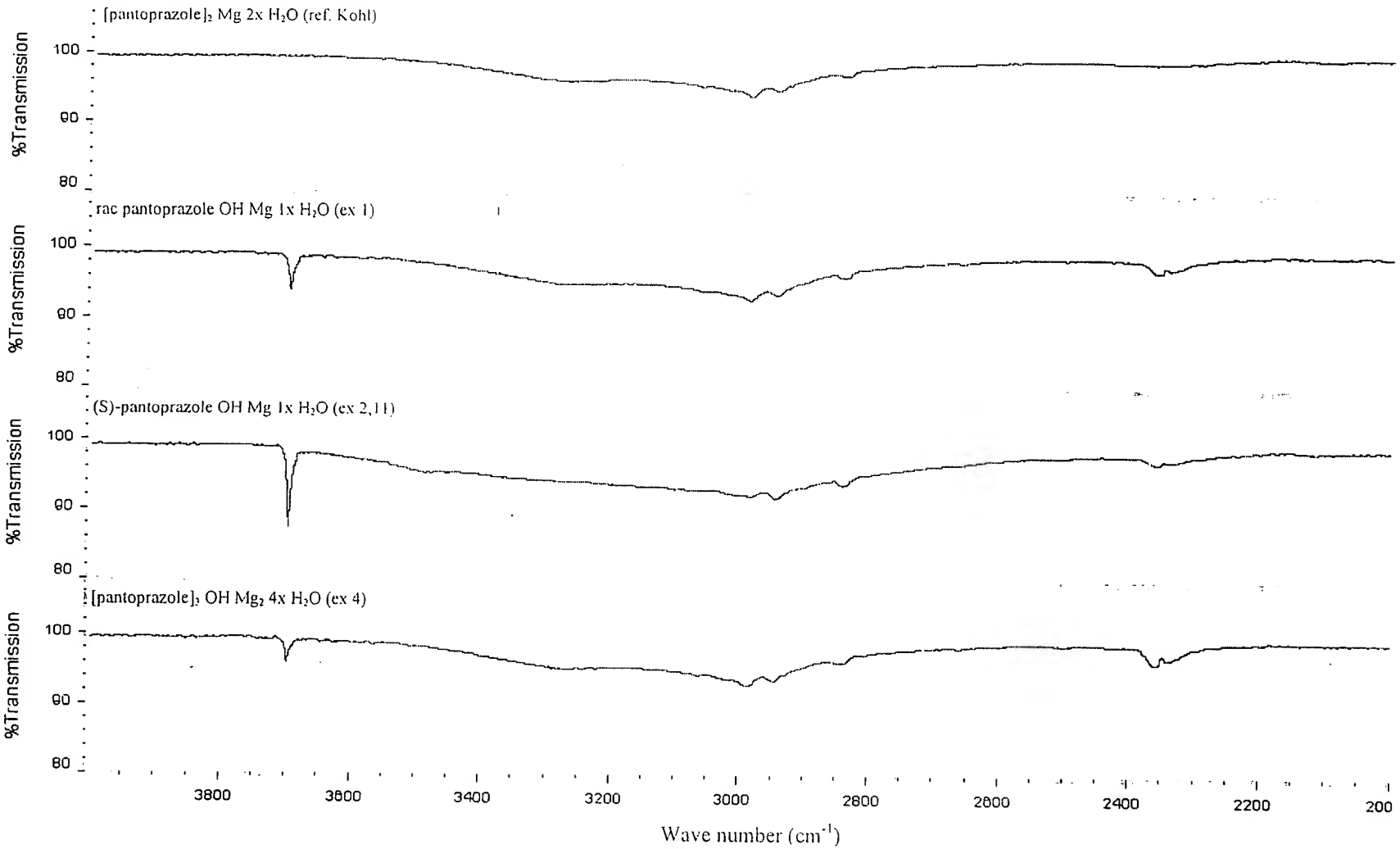
.....

Dr. Bernd Müller

EXHIBIT B

(attached herewith – 2 pages)


[pantoprazole]2 Mg 2x H2O (ref. Kohl)
rac pantoprazole OH Mg 1x H2O (ex 1)
(S)-pantoprazole OH Mg 1x H2O (ex 2.11)
[pantoprazole]3 OH Mg2 4x H2O (ex 4)
%Transmission
100
80
60
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
Wave number (cm-1)


[pantoprazole]2 Mg 2x H2O (ref. Kohl)
rac pantoprazole OH Mg 1x H2O (ex 1)
(S)-pantoprazole OH Mg 1x H2O (ex 2,11)
[pantoprazole]2 OH Mg2 4x H2O (ex 4)
%Transmission
100
90
80
3800
3600
3400
3200
3000
2800
2600
2400
2200
200
Wave number (cm-1)